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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/784,089	MEYERS ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 7-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/927,112, now issued as US Patent No. 6,897,056.

The preliminary amendment filed on February 20, 2004, amending page 1 of the specification, has been entered. The amendment was filed to update the continuity data. Therefore, the amendment contains no new matter.

Claims 1-23 are pending. Claims 4-5 and 7-23 are withdrawn. Claims 1-3 and 6 are under consideration.

Election/Restrictions

Applicant's election of Group I (claims 1-3 and 6) in the reply filed on August 8, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-5 and 7-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 8, 2006.

Priority

Applicants' claim to domestic priority under 35 USC 121 to US non-provisional application 09/927,112, filed August 10, 2001, is acknowledged. Applicants' claim to domestic priority under 35 USC 119(e) to US provisional application 60/246,808, filed

November 8, 2000, is acknowledged. The sequences of SEQ ID NOs: 1-3 of the instant application are disclosed in Figures 1a-1c.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 20, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. The references cited on the form PTO/SB08A and PTO/SB/08B of the instant application were previously submitted in its parent application, 09/927,112. An initialed form PTO/SB08A and form PTO/SB/08B are attached.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application (09/927,112) that has matured into a US patent (U.S. Patent No. 6,897,056). Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: -- A Polynucleotide Encoding a Phospholipase C-- .

The disclosure is objected to because it contains many embedded hyperlink and/or other form of browser-executable code throughout the specification, pages 7, 8, 12, 13, 14, for example. Applicant is required to delete all the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

The specification is objected to for the recitation of "plasmid deposited with ATCC Accession Number _____", which occurs throughout the specification, see for example, page 1, line 9. Appropriate correction is required by providing the ATCC Accession Number.

Section headings in the instant application are underlined and bold typed. However, section headings should appear in upper case, without underlining or bold type, see MPEP 608.01(a). Appropriate correction is required.

The specification is objected to for having a blank space at the bottom of page 69.

The use of the trademark "pMAL" and "TagMan" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as

trademarks. Applicant's cooperation is requested in reviewing the specification for additional trademarks that may be present in the specification and making the appropriate

Claim Objections

Claims 1 and 6 are objected to because of the following informalities:

Claims 1 and 6 recite the phrase "cDNA insert of the plasmid deposited with the ATCC as Accession Number _____". Appropriate correction is required by providing the ATCC Accession Number.

Claim 1 recites the term "DNA" instead of "cDNA", lines 5, 8 and 26. Amending the claims to recite "cDNA" would overcome the rejection.

Appropriate correction is required.

Claim 1 is objected to due to the recitation of "32544 nucleic acid molecule". Abbreviation/acronym/short hand notation unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation/acronym is used. It appears that applicants are using "32544" as a short notation for "phospholipase", according to the specification on page 1, lines 25-27. While applicants can be their own lexicographers, since the term "32544" is not obvious and/or commonly used in the art, in order to improve the clarity or precision of the language used, the term should not be recited in the claims without at least once reciting the entire phrase for which the shorthand notation is used.

Claim 1 is also objected to for recitation of two nucleic acid molecules, part c) and part g), of identical subject matter and written in the same exact language.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 2-3 and 6 depending therefore are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "hybridizes... under stringent conditions". The metes and bounds of the phrase are not clear in the context of the claims. While "stringent conditions" are disclosed in the specification (pages 28, line 22 through page 29, line 11), it is unclear as to which of these conditions, if any, are meant as being a "stringent condition". Therefore, it is not clear to the Examiner as to what hybridization conditions are encompassed in the phrase. Examiner requests clarification of the above phrase by amending the phrase to recite a specific stringent condition.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "32544 nucleic acid molecule". The metes and bounds of the term in the context of the claim are unclear. It appears that applicants are using "32544" as a short notation for "phospholipase", according to the specification on page 1, lines 25-27. However, it is unclear if "32544 nucleic acid molecule" encodes a polypeptide having phospholipase activity since enzymatic activity is a property of a polypeptide not a polynucleotide and since the term "32544" is not obvious and/or commonly used in the art. Therefore, the examiner has broadly interpreted "32544 nucleic acid molecule" to encompass polynucleotides encoding polypeptides having any function. However, if applicants' intended meaning of the term is different from the examiner's interpretations as stated above, applicants are requested to so state and clarify the record. For example, applicants can overcome the rejection by amending claim to recite "An isolated nucleic acid molecule encoding a polypeptide having phospholipase activity".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to **(A)** a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3, **(B)** a polynucleotide comprising a fragment of at least 15

nucleotides of SEQ ID NO:1 or SEQ ID NO:3 , **(C)** a polynucleotide encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO:2, **(D)** a polynucleotide encoding a naturally allelic variant of SEQ DI NO:2 and hybridizing to SEQ ID NO:1 or SEQ ID NO:3 or a complement thereof, and **(E)** host cell comprising the polynucleotide of **(A)-(C)** or **(D),** wherein the function of the encoded polypeptides of the polynucleotides of **(A)-(D)** are not recited. Examiner notes that since the ATCC Accession Number is missing, Examiner is interpreting "cDNA insert of the plasmid deposited with the ATCC as Accession Number _____" as being SEQ ID NO:3, which is the cDNA encoding SEQ ID NO:2.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, a sequence that is "a complement" does not read on a sequence that is a "complement" to the full length of a given sequence, but to as little as two contiguous nucleic acids. Thus, the polynucleotides of (D) have been construed as meaning polynucleotides that hybridize to as few as two contiguous nucleic acids that is a complement of SEQ ID NO:1 or 3. Further, regarding claim 1, the examiner has broadly interpreted "32544 nucleic acid molecule" to encompass polynucleotides encoding polypeptides having any function. . (See the rejection of the term "32544 nucleic acid molecule" under 35 USC 112, 2nd paragraph, for Examiner's interpretation of the term.) Therefore, claim 1 encompasses polynucleotides encoding polypeptides having any function.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise

definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims are drawn to polynucleotides encoding many functionally unrelated polypeptides encompassed within the scope of these clams, including partial sequences, resulting in a substantial variation within the genus. The genus of these polynucleotides comprise a large variable genus with the potentiality of encompassing many different polynucleotides encoding many different polypeptides having different activity or no activity. The specification only describes one species, a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO:2 and having phospholipase activity. The specification fails to describe additional representative species of the polynucleotides by any identifying characteristics or properties of the polynucleotides, for which no predictability of function is apparent.

Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

The claims also encompass polynucleotides encoding naturally occurring allelic variants of SEQ ID NO:2. The specification defines "naturally occurring allelic sequence" (page 8) as an alternative form of the gene which may result in at least one mutation in the nucleic acid sequence, which are found in nature (page 38, line 11 through page 39, line 15. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. This definition does not provide any specific information about the structure of polynucleotides encoding naturally occurring (alleles) variants of SEQ ID NO:2 (i.e. where in the regions within which mutations are likely to occur) nor discloses any function for the naturally occurring variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any naturally occurring alleles. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art, structure of one does not provide guidance to the structure others.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1, 3 and 6.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 3 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel plasmid. Since the plasmid is essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmid's sequence is not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the plasmid. The specification does not disclose a repeatable process to obtain the plasmid and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of the plasmid should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that if applicants have deposited the plasmid, it must be public available. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that: 1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request; 2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808; 3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and 4. the deposit will be replaced if it should ever become inviable.

Claims 1, 3 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 or 3 encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2 and having phospholipase activity, host cell comprising said polynucleotide and a method of producing said polypeptide, does not reasonably provide enablement for **(A)** a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3, **(B)** a polynucleotide comprising a fragment of at least 15 nucleotides of SEQ ID NO:1 or SEQ ID NO:3 , **(C)** a polynucleotide encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO:2, **(D)** a polynucleotide encoding a naturally occurring allelic variant of SEQ DI NO:2 and hybridizing to SEQ ID NO:1 or SEQ ID NO:3 or a complement thereof, and **(E)** host cell comprising the polynucleotide of **(A)-(C)** or **(D),** wherein polynucleotides of **(A)-(D)** have unknown structure and

encode polypeptides having unknown function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to **A)** a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3, **(B)** a polynucleotide comprising a fragment of at least 15 nucleotides of SEQ ID NO:1 or SEQ ID NO:3 , **(C)** a polynucleotide encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO:2, **(D)** a polynucleotide encoding a naturally allelic variant of SEQ DI NO:2 and hybridizing to SEQ ID NO:1 or SEQ ID NO:3 or a complement thereof, and **(E)** host cell comprising the polynucleotide of **(A)-(C)** or **(D),** wherein the function of the encoded polypeptide by the polynucleotides of **(A)-(D)** is not recited. Examiner notes that since the ATCC Accession Number is missing, Examiner is interpreting "cDNA insert of the plasmid deposited with the ATCC as Accession Number _____" as being SEQ ID NO:3, which is the cDNA encoding SEQ ID NO:2.

The breadth of the claims.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, a sequence that is "a complement" does not read on a sequence that is a "complement" to the full length of a given sequence, but to as little as two contiguous nucleic acids. Thus, the polynucleotides of (D) have been construed as meaning polynucleotides that hybridize to as few as two contiguous nucleic acids that is a complement of SEQ ID NO:1 or 3. Further, regarding claim 1, the examiner has broadly interpreted "32544 nucleic acid molecule" to encompass polynucleotides encoding polypeptides having any function. . (See the rejection of the term "32544 nucleic acid molecule" under 35 USC 112, 2nd paragraph, for Examiner's interpretation of the term.). Therefore, claim 1 encompasses polynucleotides encoding polypeptides having any function. Regarding claim 3, since the specification contemplates transgenic animals expressing the claimed polynucleotides (page 54, line 24 through page 54, line 22), in its broadest reasonable interpretation, claim 3 is directed to both host cells and host cells within a transgenic animal.

Therefore, claims 1, 3 and 6 are drawn **(A)** a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3, **(B)** a polynucleotide comprising a fragment of at least 15 nucleotides of SEQ ID NO:1 or SEQ ID NO:3 , **(C)** a polynucleotide encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO:2, **(D)** a polynucleotide encoding a naturally allelic variant of SEQ DI NO:2 and hybridizing under any conditions to SEQ ID NO:1 or SEQ ID NO:3 or a complement thereof (as little as two nucleotides), and **(E)** host cell comprising the polynucleotide of **(A)-(C)** or **(D)** or

said host cell within a transgenic animal comprising, wherein polynucleotides of **(A)-(D)** have unknown structure and encode polypeptides having unknown function.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotide encoding polypeptides of virtually any structure and/or function or polynucleotides/fragments having virtually any structure and/or function. In the instant case, the specification enables the polynucleotides of SEQ ID NO:1 or 3 encoding a polypeptide having the amino acid sequence of SEQ ID NO: 2 having phospholipase C activity and a method of producing said polypeptide. Regarding claim 3, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of transgenic animals. The specification fails to teach how to generate or how to use such transgenic animals. In the instant case, the specification enables only an isolated host cell transformed with polynucleotide encoding the polypeptide of SEQ ID NO:2.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for variants comprising multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within the encoded protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition,

one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, while the skilled artisan can produce variants of the polypeptide of SEQ ID NO:2 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine due to the fact that the number of species encompassed by the claims is extremely large. For example, Guo et al.(*Proc Natl Acad Sci USA*. 2004 Jun 22;101(25):9205-10 – form PTO-892) teaches that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% (*x* factor) and that this number appears to be consistent with other studies in other proteins as well (Abstract). Guo et al. further shows in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ x 100% where x is the number of mutations introduced and 0.66 is the probability of a protein to remain active after one amino acid change (0.66= 1-0.34). If one were to apply this estimate to the instant case, for polynucleotides encoding polypeptides having 60% sequence identity to SEQ ID NO: 3 (1207 amino acids; 483 mismatches = 0.40x1204), only $(.66)^{483}$ x 100% or 6.9 x 10^{-86}% of random mutants having 60% sequence identity to SEQ ID NO:2 would be active. As indicated above, 60% sequence identity to SEQ ID NO: 2 allows for 483 amino acid changes. Therefore, to find a single active mutant within random mutants having 60% sequence identity to SEQ ID NO:3, one of skill in the art would have to screen close to over a gargantuan number of mutants (100/6.9 x 10^{-86}%). For a polypeptide encoded by a fragment that comprises of at least **15** nucleotides, or a polypeptide having less than 2%

(15/1207x100%) sequence identity to SEQ ID NO:2, and polynucleotides hybridizing to "a complement" of SEQ ID NO:1 or 3, as little as **two** nucleotides, to find a single active mutant, it would be an almost impossible undertaking to one having ordinary skill in the art and the above calculations would be superfluous.

In the absence of: (a) rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function, (b) a correlation between structure and phospholipase C activity, the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. One of skill in the art would have to test these infinite possible polynucleotides/polypeptides to determine (1) which ones have phospholipase C activity or which ones encode polypeptides having phospholipase C activity, (2) the specific substrates targeted by such proteins and (3) how to use those polynucleotides encompasses by the claims which do not encode polypeptides having phospholipase C activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance which respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Regarding claim 3, given the unpredictability of expressing transgenes in animals, lack of guidance provided by the specification and absences of any working

examples, it would require undue experimentation to make any transgenic animals comprising the polynucleotides recited in claim 1.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In the instant case, neither the specification or the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any polynucleotides encoding polypeptides having the same biological function as that of the polypeptide of SEQ ID NO:2 or predict the function of a polynucleotide/polypeptide from its primary structure. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within the polypeptides encoded by SEQ ID NO: 1 or 3 can be modified and which ones are conserved such that one of skill in the art can make the recited polynucleotides encoding polypeptides having the same biological activity as that of the polypeptide of SEQ ID NO:2, (2) which segments of the encoded polypeptide of SEQ ID NO:2 are essential for activity, and (3) the general tolerance of phospholipase C proteins to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein

are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

Further, the function of a polypeptide cannot be predicted from its structure and the specification does not teach how to use polypeptides having any function or having no activity. The quantity of experimentation in this area is extremely large since there is significant variability in the activity of the polynucleotides in the claims. It would require significant study to identify the actual function of the encoded polypeptides and identifying a use for the encoded polypeptide would be an inventive, unpredictable and difficult undertaking. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found

for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides.

Regarding claim 3, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3 :548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549). Furthermore, Mullins et al. (Hypertension 22(4):630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631).

The amount of direction or guidance presented and the existence of working examples.

The specification discloses only the polynucleotides of SEQ ID NO:1 or 3 encoding a polypeptide having the amino acid sequence of SEQ ID NO:2 having phospholipase C activity and a method of producing said polypeptide. However, the speciation fails to provide any information as to (1) specific substrates associated with polynucleotides encoding phospholipase C of SEQ ID NO:2, (2) structural elements required in a polypeptide having phospholipase C 1 activity, or (3) which are the structural elements in the polypeptide of SEQ ID NO:2 that are essential to display phospholipase C activity. No correlation between structure and function of having phospholipase C activity has been presented. There is no information or guidance as to which amino acid residues in the polypeptides encoded by SEQ ID NO: 1 or 3 can be

modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2.

Regarding claim 3, the specification discloses host cells transformed with polynucleotides hybridizing or having homology to SEQ ID NO:1 or 3. However, the speciation fails to provide any specific methods of successfully expressing said polynucleotides in an animal. The specification also fails to provide any working examples of transgenic animals expressing said polynucleotides.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability of the prior art in regard to structural changes and their effect on function and the lack of knowledge about a correlation between structure and function, an undue experimentation would be necessary one having ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a polynucleotide encoding polypeptides having the desired biological characteristics recited in the claim and transgenic animals expressing said polynucleotides are unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Seki et al.

Claim 1 is drawn to a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 of the instant invention.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly interpreted "32544 nucleic acid molecule" to encompass polynucleotides

encoding polypeptides having any function. (See the rejection of the term "32544 nucleic acid molecule" under 35 USC 112, 2nd paragraph, for Examiner's interpretation of the term.

Seki et al. (DNA Res. 1997 Oct 31;4(5):345-9 – form PTO-892) discloses a polynucleotide having 92.1% sequence identity to SEQ ID NO:3 and having 72% sequence identity to SEQ ID NO:1of the instant invention, wherein said polynucleotide encodes a polypeptide having 91.7% sequence identity to SEQ ID NO:2 of the instant invention (see Table 1 "Gene number 0450" and see attached sequence alignments "Seki et al."). Therefore, the reference of Seki et al. anticipates claim 1.

Claims 1, 3 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Das et al.

Claims 1, 3 and 6 are drawn to a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 of the instant invention, host cell comprising said polynucleotide and a method of producing a polypeptide encoded by said polynucleotide.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly interpreted "32544 nucleic acid molecule" to encompass polynucleotides encoding polypeptides having any function. (See the rejection of the term "32544 nucleic acid molecule" under 35 USC 112, 2nd paragraph, for Examiner's interpretation of the term.

Das et al. (US Patent Application Publication No. US 2004/0023354 A1 – form PTO-892) discloses a polynucleotide having 90.2% sequence identity to SEQ ID NO:3

and having 79.5% sequence identity to SEQ ID NO:1of the instant invention, wherein said polynucleotide encodes a polypeptide having 95.5% sequence identity to SEQ ID NO:2 of the instant invention (see pages 5, paragraphs [0040]-[0043], 54-57 and 64-65 of US 2004/0023354 A1 and see attached sequence alignments "Das et al."). Therefore, the reference of Das et al. anticipates claims 1, 3 and 6.

Claims 1, 3 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyers et al.

Claims 1, 3 and 6 are drawn to a polynucleotide comprising at least 15 nucleotides of SEQ ID NO:1 or 3 of the instant invention, host cell comprising said polynucleotide and a method of producing a polypeptide encoded by said polynucleotide. The examiner has interpreted "32544 nucleic acid molecule" to encompass polynucleotides encoding polypeptides having phospholipase C activity. (See the rejection of the term "32544 nucleic acid molecule" under 35 USC 112, 2nd paragraph, for Examiner's interpretation of the term.)

Meyers et al. (US Patent 6,534,301 B2 – form PTO-892) discloses a polynucleotide encoding a polypeptide having phospholipase C activity, wherein said polynucleotide comprises at least 15 nucleotides of SEQ ID NO:1 or 3 of the instant invention, host cell comprising said polynucleotide and a method of producing said polypeptide (see Figure 1 and Column 32, line 57 through Column 36, line 11 and see attached sequence alignments "Meyers et al"). Therefore, the reference of Meyer et al. anticipates claims 1, 3 and 6.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seki et al. in view of Itakura.

Claims 3 and 6 are drawn to a host cell comprising a polynucleotide having at least 60% sequence identity to SEQ ID NO:1 of the instant invention and a method of producing a polypeptide encoded by said polynucleotide.

Seki et al. (DNA Res. 1997 Oct 31;4(5):345-9 – form PTO-892) discloses a polynucleotide having 92.1% sequence identity to SEQ ID NO:3 and having 72% sequence identity to SEQ ID NO:1of the instant invention, wherein said polynucleotide encodes a polypeptide having 91.7% sequence identity to SEQ ID NO:2 of the instant invention (see Table 1 "Gene number 0450" and see attached sequence alignments "Seki et al."), as discussed above. Seki et al. also teaches that said polynucleotide comprises an open reading frame and an *in vitro* transcription/translation assay system generated a protein signal. The difference between the reference of Seki et al. and the instant invention is that the reference of Seki et al. does not teach a host cell comprising said polynucleotide of Seki et al. nor a method of producing a polypeptide encoded by said polynucleotide by culturing said host cell.

However, expression of mammalian genes in host cells and production of their encoded polypeptides are well known in the art. Itakura (US Patent No. 4,571,421) discloses a method of expressing a mammalian gene in a host cell and producing its encoded polypeptide by culturing said host cell (abstract and Column 4, line 12 through line 55).

Therefore, in combining the teachings of Seki et al. and Itakura, it would have been obvious to one having ordinary skill in the art at the time the invention was made

to transform a host cell with the polynucleotide of Seki et al. and produce the polypeptide encoded by the polynucleotide of Seki et al. using the method taught by Itakura. One of ordinary skill in the art would have been motivated to make such a host cell and express the protein encoded by the polynucleotide of Seki et al. for the benefit of producing said protein for characterization. One of ordinary skill in the art would have had a reasonable expectation of success of transforming the host cell and producing said protein since Itakura teaches transformation of host cells with mammalian genes and a method of producing proteins encoded by said genes by culturing said host cells and since Seki et al. teaches that the polynucleotide having homology to SEQ ID NO:1 and 3 of the instant invention encodes a protein.

Therefore, the above references render claims 3 and 6 *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U. S. Patent No. 6,897,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: Claims 1-3 and 6 of the instant application and claims 1-15 of U.S. Patent No. 6,897,056 are both directed to a polynucleotide encoding a polypeptide having SEQ ID NO:2, host cell comprising said polynucleotide and a method of producing said polypeptide. The polynucleotide of SEQ ID NO: 1 and its encoded polypeptide of SEQ ID NO: 2 of the instant application are 100% identical to the polynucleotide of SEQ ID NO:1 and its encoded polypeptide of SEQ ID NO:2 of U.S. Patent No. 6,897,056 (see attached sequence alignments "U.S. Patent No. 6,897,056").

Claims 1-3 and 6 of the instant application are drawn to a polynucleotide having at least 60-100% sequence identity to SEQ ID NO: 1 or 3, polynucleotide comprising a fragment of at least 15 nucleotides, polynucleotide encoding a polypeptide of SEQ ID NO:2 or fragments thereof, polynucleotide encoding a naturally occurring allelic variant of SEQ ID NO:2, host cell comprising said polynucleotide and a method of producing said polypeptide. Claims 1-15 of U. S. Patent No. 6,897,056 are drawn to a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, host cell comprising said polynucleotide and a method of producing said polypeptide. A polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3, polynucleotide comprising a fragment of SEQ ID NO:1 or 3, a polynucleotide encoding a fragment of SEQ ID NO:2, polynucleotide encoding a naturally occurring allelic variant of SEQ ID NO:2 are

specific embodiments of the polynucleotides described in the reference patent. The specification of the reference patent supports a polynucleotide having at least 60-100% sequence identity to SEQ ID NO: 1 or 3, polynucleotide comprising a fragment of at least 15 nucleotides, polynucleotide encoding a polypeptide of SEQ ID NO:2 or fragments thereof, polynucleotide encoding a naturally occurring allelic variant of SEQ ID NO:2, host cell comprising said polynucleotide and a method of producing said polypeptide (Columns 1-2) that would anticipate the polynucleotide of claims 1-2, host cell of claim 3 and the method of claim 6. Claims 1-3 and 6 of the instant application cannot be considered patentably distinct over claims 1-15 of the reference application when there is specifically recited embodiment that would anticipate claims 1-3 and 6 of the instant application. Alternatively, claims 1-3 and 6 of the instant application cannot be considered patentably distinct over claims 1-15 of the reference patent because it would have been obvious to one having ordinary skill in the art to modify claims 1-15 of the reference patent by selecting a specifically disclosed embodiment that supports those claimed, i.e. polynucleotide having at least 60% sequence identity to SEQ ID NO:1 or 3. One of ordinary skill in the art would have been motivated to do this because the embodiments claimed in the instant claims are disclosed as being a preferred embodiment within claims 1-15 of the reference patent. Therefore, the conflicting claims are not patentably distinct from each other.

Conclusion

Claims 1-3 and 6 are rejected.

None of the claims are allowable.

Examiner Comment

In this case, there is no dispute that the polypeptide of SEQ ID NO:2 has phospholipase C activity, particularly as the specification discloses that SEQ ID NO:2 exhibits such activity (page 1, lines 25-26 and page 43, lines 26-30). Further, polypeptides having phospholipase C activity such as the polypeptide of SEQ ID NO:2 have a well-established utility in hydrolysis of phospholipids (see, e.g. US Patent 6,534,301 B2 and US Patent 5,474,921).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak
Patent Examiner 1652